RESEARCH ARTICLE

Epidemiological Correlates of Breast Cancer in South India

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Abstract

Background: Breast cancer is the most frequent cancer in women globally and represents the second leading cause of cancer death among women (after lung cancer). India is going through epidemiologic transition. It is reported that the incidence of breast cancer is rising rapidly as a result of changes in reproductive risk factors, dietary habits and increasing life expectancy, acting in concert with genetic factors. Materials and Methods: In order to understand the existing epidemiological correlates of breast cancer in South India, a systematic review of evidence available on epidemiologic correlates of breast cancer addressing incidence, prevalence, and associated factors like age, reproductive factors, cultural and religious factors was performed with specific focus on screening procedures in southern India. Results: An increase in breast cancer incidence due to various modifiable risk factors was noted, especially in women over 40 years of age, with late stage of presentation, lack of awareness about screening, costs, fear and stigma associated with the disease serving as major barriers for early presentation. Conclusions: Educational strategies should be aimed at modifying the life style, early planning of pregnancy, promoting breast feeding and physical activity. It is very important to obtain reliable data for planning policies, decision-making and setting up the priorities.

Keywords: Breast cancer - epidemiology - South India

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Introduction

Breast cancer is the most frequent cancer in women globally and represents the second leading cause of cancer death among women (after lung cancer) (Chandra, 1979; Dumitrescu and Cotarla, 2005). Genetic predisposition accounts for approximately 5-10% of all breast cancers. Mutations in two autosomal dominant genes, BRCA1 and BRCA2 have been linked to familial breast cancer (Hall et al., 1990).

India is going through epidemiologic transition. It is reported that the incidence of breast cancer is rising rapidly in India as a result of changes in reproductive risk factors, dietary habits and increasing life expectancy (Yeole and Kurkure, 2003). The available estimates suggests that approximately 75,000 new cases occur in Indian women every year (Chopra, 2001). This might be a gross underestimate given that there is paucity of information available on incidence, prevalence and other epidemiologic correlates of breast cancer in India. The available estimates are incomplete, limited to few areas and have several methodological problems (ICMR, 2010). The pooled data from five metropolitan cities indicated that there has been approximately an 119% change in the number of Breast cancer cases among (Takiar and Vijay, 2010) (Increase in cancers of breast in 2003-05 compared to 1998-90). Part of this can be explained by improved collection of data and enhanced awareness and screening. However, this does also may indicate the growing incidence of breast cancer in the country, suggesting a 0.5% in rise in incidence every year (Dikshit et al., 2012). The report in Lancet by Rajesh Dikshit et al states, "In women aged 30-69 years, breast cancer affects 10·2% of all cancer mortalities". This article also mentions that in women, breast cancer mortality was similar in rural and urban India. Breast cancer is probable to be diagnosed at earlier stages in urban women than in rural women and consequently more treatable. Trends recorded in urban cancer registries show increases in the incidence of breast cancer of about 0.5% per year from 1991-2005 (Table 1), and an increase in the proportion presenting with localized breast cancer (Dhillon et al., 2011). Also, low-cost treatments, such as Tamoxifen with surgery for early stage breast cancer, have helped to substantially reduce the breast cancer mortality rates in the developed countries and similar results in India might have reduced the prevalence in urban areas (Peto et al., 2000) but not in urban areas (Dikshit et al., 2012).

The available evidence does not provide useful interpretations for identifying local prevalence of breast

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Table 2. Description of Included Studies Qualitative Synthesis

Author, Year	Age group of women (years)	Location	OR	Risk factor measured for Breast cancer	Confounders controlled	Selection bias mentioned and controlled	Measurement error mentioned and controlled
Case Control Studies-10							
Surekha, 2010[a]	NM	Hyderabad	OR-1.706	Cyp17 gene polymorphism	No	Yes	NM
Vaidyanathan, 2009[b]	42 (mean age) Age range 16-68	Different parts of South India		BRCA1 and BRCA2 gene mutations	No	Not controlled	NM
Volga and Syamala, 2009	20-79	Thiruvananthapuram	OR for familial cases 0.61 (N=140) OR for sporadic (N-219) breast cancer-patients is 0.97	XPD (Lys 751Gln) and XRCC1 (Arg 399Gln) genes polymorphism	No	Not controlled	
Mathew, 2008	NM	Trivandrum (Kerala) and Chennai	OR for BMI>25, waist size>85cm and hip size >100 cm (Premenoupausal women) =1.24(0.96-1.62) and Post-menopausal women OR=1.61 91.2202.12)	Anthropometric factors -Height, BMI, Waist to hip ratio,Body size,Body size, current body size, (N=1866)	Yes	Mentioned not controlled	Yes
Syamala, 2008	<50	Thiruvananthapuram (Kerala)	OR of Normal and mutated BRCA2 genes 1 (average for all factors) BRCA2 positive mutaltions cause 44.4% mortatity due to BC (N=102)	BRCA2 gene mutations on hereditary breast cancer risk (factors studied Tumour size, Node, Metastatis,Stage, Laterality, ER Status, PR status, Grade)	No	Not controlled	yes
Volga and Syamala, 2007	20-79	Thiruvananthapuram (South India)	OR for GSTM1 genes for Familiar BC patients = 2.0 (1.25-3.13) ((N=597) and for Sporadic BC= 2.3 (1.3-3.871.)(N=125) AND OR for GSTT1 deletion was found to be more frequent among sporadic breast cancer patients (OR=1.850 (0.966-3.542) tthan those with familial breast cancer	Polymorphism of GSTs in familial and sporadic bresat cancers	No	Mentioned but not controlled	Mentioned but nor controllled
Gajalakshmi and Shanta, 1990	NM	Madras	Premenopausal women ORs for diff risk factors., Age at menarche (13.7 yrs N= 238)-1.1 (0.4-1.3 Marital status- Married OR- 1 and single=5.3, Nulliparity OR=2.9 (1.6-5.2) , Age at marriage (mean age 17.8 yrs) OR= 10.2, Age at first birth (excluding nulliparous women) highest for >25 yrs OR=2.6 (1.2-5.3), Diff between first birth and menarche (OR highest of >12 yrs, OR=3.1 (1.4-6.7) and OR higher for less number of children OR=1.8 (1.1-3.1) Post menopausal women OR higher among 44-46 yrs OR=2.8,(1.7-4.5),47-49 OR=2.9 (1.8-4.7)	Both Premenopausal and Post menopausal women (Age at menarche, Marital status, Nulliparity, Mage at first child birth, No of children)	No	Mentioned and controlled	Not Controleld
Gajalakshmi et al., 2008	(patients with primary breast cancer only)	Chennai and Trivandrum	Among Premenopausal women,No Breast feeding OR=1.6 (0.74-3.45)compared to ever breast feeding which has OR=1(N=1866) Post menopausal Women OR= 3.29 (0.69-15.6)	Breast feeding, age at menarche, age at first child birth, parity, History and duration of breast feeding, no, of children breast fed, age at menopause with breast cancer risk	No	Mentioned not controlled, Controls were female visitors to patients with breast cancer	Mentioned but not controlled
Gajalakshmi and Harrison, 2010	≥25	Manipal	OR for Non veg diet is 1.94 (N=63 cases) (not statistically significant)	Socio demographis characteristics, reproductive factors, type of diet, physical activity, method of identification of disease, mode of referral	Mentioned not controlled	Mentioned not controlled	Mentioned Not controlled
Dey, 2009		Trivandrum (Kerala) and Chennai	ER-was 64% among among BC patients (N=900)	Risk factors accoridng to Estrogen receptor status	yes	yes	yes

Table 2 (continue). Description of Included Studies Qualitative Synthesis

Author, Year	Age group of women (years)	Location	OR	Risk factor measured for Breast cancer	Confounders controlled	Selection bias mentioned and controlled	Measurement error mentioned and controlled
Cross Sectional Study-1							
Kuraparthy, 2007	NM	Tirupati	Survival rate 50.8 months. 3 year survival period 70%	Survival rates mesured for various risk factors like HR status, Menopause, Abortion,OCP,Breast feeding,Family history Education, Diabeted, mixed diet	No	Yes	Yes
Secondary data analysis (cancer registries) retrospective data analysis)-4							
Nandakumar, 1998	All ages	Bangalore	% Survival rates for 5 years *OS=41.7 and RS=46.1) (N=1381) and Age standardised relative survival (ASRS)=40.4	Surviva; rates (observed and relative survival rate			
Ali, 2007	19-95	Kerala and Chennai	Elevated risk of late stage diagnosis among unmaried women, (OR=3.31; (: 1.10-9.96), N=522), among widowed,divorced, ((OR=1.46; 95% CI: 0.89-2.37) women with lower education (OR=2.72; 95% CI: 1.06-7.03 for illiterate women, OR=2.32; 95%CI: 1.05-5.13 for women with primary school education and OR=2.07; 95%CI: 1.02-4.21	Socio economic and demographic factors in delayed presentation	No	NM	Yes Not controlled
Chauhan, 2011[c]	Mean Age=45 (min:max-23:46)	Coastal Karnataka	Peak incidence noticed in 35-39 yrs and in (N=112) and 50-54 yrs age group	Age of incidence of Breast cancer	No	Yes	NM
Yeole, 2003[*]	All ages	Bangalore and Chenna		Age Adjusted Incidence Rates			
Nested Case Control study (Cohort)-1							
Jayalekshmi, 2009	NM	Karunagapally (Kerala)	Tapioca Consumption for more than 3 times a day was found to be associated with reduciotn in 50 % risk (OR=1 Vs 0. vs 0.55)(N=264)Average age at diagnosis is 46.4	Sociodemographic and Reproductive characteristics and Dietary variables	No	Controlled	NO

[*]Incidence: AAIR for Bangalore is 2.14 ($p<0.005$) and Chennai is 1.21 ($p<0.001$); Prevalence of [a]24.6% (N=61): [b]68.7% (N=249 cases: [c]11%

cancer and plan public health actions according. It is not possible to answer one putative question: whether breast cancer is highly prevalent in south India, as we just do not have sufficient information to tackle this question.

In order to understand the epidemiological correlates, we conducted a systematic review of evidence available on epidemiologic correlates of breast cancer addressing incidence, prevalence, and associated factors like age, reproductive factors, cultural and religious factors with specific focus on screening procedures in southern India. The objective of this paper is to do a qualitative synthesis of epidemiologic correlates from studies conducted in South India on epidemiological correlates of breast cancer (age, reproductive factors, religious factors etc on the incidence and prevalence) including screening methods.

Materials and Methods

A comprehensive systematic review was conducted with predefined review protocol developed by the reviewer. The inclusion criteria were that the studies should have be either Cohort, Case control or Cross sectional studies studying Breast cancer Women from India, wherein the outcome was either risk assessment, mortality or survival rates from breast cancer. The exclusion criteria were Case studies, Review Articles or study population being other Asian/Indian women living in other countries or any type of Clinical Interventions (Drug, Chemotherapy, Radiotherapy). We conducted complete search of all the articles

Search strategy

The search was done from: 1946 to 2012 in the data bases Ovid SP, Medline and the period of search was from 1980 to 2012. We used a broad search Strategy. Preliminary Search was conducted using the key words "Breast Cancer" AND "India"-yielded 1612 records. The search was refined using the terms "Breast Cancer" AND "Risk" AND "India" Time period mentioned was from the beginning of data availability in the database till 2012 (in chronological order). Language mentioned was English Further filter was done on type of Studies to be included. The search yielded 105 records (from Ovid SP database and Medline). Exact

process was carried out in Embase database yielded 25 records.

Extraction of data

As the first step, we included articles with title and abstract fulfilling the inclusion criteria. Several studies were excluded during this phase. We also included 20 articles based on the consultation with experts and authors of earlier systematic reviews. We crosschecked with other databases and earlier reviews to include further articles. During the next step, we downloaded the full text of the articles for review. We extracted the following information from the full texts: First author, year, country, study settings such as whether occupational or community based, age, gender, occupation, sample characteristics, study design employed, inclusion criteria by authors, we assessed the quality of the studies by keeping. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Moher et al., 2009a) guidelines as reference. The aim of these guidelines is to help authors report a wide array of systematic reviews to assess the benefits and harms of a health care intervention. PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses (Moher et al., 2009a).

Results

Search results: the initial search identified n=1612 studies. We obtained 27 additional records from other database and two systematic reviews which were not identified through our initial search 0.367 of the 1639 studies were included for further assessment. Further filter using the search key for required study designs yielded 130 records. We cross checked for earlier systematic reviews and included 2 articles. We didn't include 32 articles due to the reasons like animal study (1), intervention (7), not conducted in India (10) not accessible (4) and other reasons like studies with mixed results,, research communications with no definite conclusions, evaluation studies etc (10).

A total of 100 full text articles were selected . After careful reading, of the abstracts, 20 full text articles of various studies on Breast cancer patients across South India were taken for the current review. After careful and thorough reading, 4 articles have been again excluded for the following reasons Full text article not available (1), Not from South India (1), Study on Families of BC patients (1), and educational intervention on screening (1). Finally 16 articles have been selected for the qualitative synthesis (Gajalakshmi and Shanta, 1991; Nandakumar et al., 1998; Yeole and Kurkure, 2003; Kuraparthy et al., 2007; Ali et al., 2008; Mathew et al., 2008; Syamala et al., 2008a; 2008b; Dey et al., 2009; Jayalekshmi et al., 2009; Syamala et al., 2009; Vaidyanathan et al., 2009; Harrison et al., 2010; Surekha et al., 2010; Chauhan et al., 2011)

Methodological qualities of included studies: Out of 16 included studies 10 were Case studies, 1 Nested case control study (on a cohort of women), 4 studies were based on Secondary data analysis and 1 (Marmot et al., 2007) was cross-sectional study. Confounding factors were reported and adjusted in 2 out of 10 case control studies, mentioned and not controlled in 3 studies and not mentioned in rest of the studies. Selection bias was mentioned and controlled in only 6 studies (2 case control studies, 1 nested case control study), 2 secondary data analysis, and 1 cross sectional study). Four out of 16 studies only reported and controlled measurement error.

Participants' characteristics

The age group of the participants ranged from 16-79 yrs. Women who have been diagnosed with breast cancer (both familial and sporadic cases) were the participants Majority (7 out of 16) of the studies were conducted in Kerala 3 were from Karnataka, and 3 from Tamilnadu and two were from Andhra Pradesh.

Measurement of outcome

Incidence and Prevalence estimates of Breast cancer reported in these studies were measured. Epidemiological correlates which have an impact on increasing the risk and mortality among breast cancer patients were measured. These included a wide range of factors as listed in table.1. The common finding was that breast cancer is generally detected at advanced stages.

Some studies discussed that menstrual and reproductive factors are associated with an increased risk of breast cancer because they may increase lifetime exposure to estrogen. Changes in menstrual and reproductive patterns among women (i.e., early age at menarche and late age at first childbirth) may have contributed to the increase in breast cancer risk, particularly among younger women. (Pakseresht et al., 2009; Lodha et al., 2011) Parity and age at first child birth: Greater number of births and early age at first full term birth (FFTB) are also found to be associated with breast cancer.

Discussion

Our study results are in confirmity with evidence that the incidence of breast cancer in developing countries is rapidly on the rise. The reported incidence rates for Breast Cancer from the National Cancer Registry Programme (NCRP) data indicate that percentage of Breast cancer relative to total cases over time in Bangalore and Chennai have increased. (ICMR) Also, projections of cancer cases in India (2010-2020) of NCRP indicate that there will be more than 100,000 estimated number of Breast Cancer cases annually in India based on the data from NCRP in Bangalore. These geographical variations in incidence and mortality rates of breast cancer suggest that the known risk factors for breast cancer may vary in different part of the country and that environmental factors are of greater importance as well as genetic factors (McPherson et al., 2000; 2006)

Cancer of breast has emerged as the leading site of cancer in most urban populations of India. For the year 2007, there have been an estimated 82,000 new cases of cancer Breast in India. It is rapidly replacing cancer of cervix as the most important leading site of cancer among women. The data collected over the years from five urban population based cancer registries namely Bangalore,

Bhopal, Chennai, Delhi and Mumbai, under the network of National Cancer Registry Programme (NCRP) have shown a statistical rising trend in the incidence rate of breast cancer. In hospital-based cancer registries, cancer of the breast is the leading site of cancer in Mumbai and Thiruvananthapuram,second leading site in Bangalore, Dibrugarh and Chennai. Cancer of breast constitutes 14.3-30% of all cancers in women in these HBCRs (Nandakumar et al., 1995).

The available literature suggests that secular changes in breast cancer have dissimilar temporal patterns for developed countries compared to southern India (Seow et al., 1996; Leung et al., 2002; Li and Daling, 2007). The incidence of breast cancer increased in developed countries such as the United States and Canada in the 1980s and 1990s and began to plateau in the late 1990s (Li et al., 2003; Althuis et al., 2005) A likely explanation given for the plateau phase of incidence was that enough proportion of women were screened through mammography method (Li and Daling, 2007). As in India, most of the Asian countries display lower but increasing trend of breast cancer over the past several decades. The predominant reason for the increasing incidence of breast cancer reason can be increase in environmental factors that include changes in dietary and fertility patterns alongside an increasingly affluent and sedentary lifestyle (Jin et al., 1999; Yip et al., 2001; Leung et al., 2002). Other reasons are lack of effective screening methods and access issues (Seow et al., 1996; Shapiro et al., 1998; Leung et al., 2002; Babu et al., 2011). The significant increasing trends for breast cancer risk might be explained by later age at first birth and lower total parity of more recent generations (Nanda et al., 1995; Sciences and ORCMacro, 2000; Sciences, 2007). In one of the largest case series study, the investigators reported a redistribution of hormone receptor expression– ER+ (7.5-10.6%) and ER+/PR+ status (25-41.8%) increasing between 1999 and 2006 while PR+ decreased (21-3.4%). All the evidence above show changing reproductive factors may have a role in the observed increasing trends. Also, an observation that women having shorter menstrual cycles (<26 days) spend more time in the luteal phase when estrogen and progesterone levels are high and when breast mitotic activity is at its peak, compared to women with longer cycle length (Kelsey et al., 1993) Various pathophysiological mechanisms were found to be responsible such as decreased frequency and intensity of ovulation thus maintaining the consistent lower level of estrogen, mobilisation of endogenous carcinogens from the ductal and lobular epithelial cell environment and facilitating the excretion of organochlorides (xenoestrogens) having the same carcinogenic potential as estrogen (Gauthier, 2003). This complex interplay of genetics and environment in genesis of breast cancer is being affected by rising trends of breast cancer incidence inspite of formulating several control strategies.

Inconsistency and heterogeneity of our estimates indicate that the absence of population-based breast cancer screening programme for women might be masking the actual incidence might be masked. There have been several reports suggesting low incidence of breast cancer among Indians. It is important to note that almost all of the population-based registries from India contain data from mostly cancers reported from conurbations of the respective city. The data from registries in India cover a population amounting to <5% of the total population of the entire country. Compared to this, other national registries provide national population-wide figures. In the absence of successful population-wide mass screening programs for cancer detection, it is erroneous to conclude that there is lower incidence of breast cancer in India. Most importantly, the cancer registries are not representative of the total population, as rural areas are mostly missed out (Babu, 2009). There is evidence available to suggest that incidence of breast cancer is same in rural areas as in urban areas (Dikshit et al., 2012). Also, it is only the late stages that get referred to urban centers. However, what happens to the data concerning all the women who might die or don't seek health care (Survival Bias: Only the survivors of the study end up being referred to tertiary hospitals). The new cases of cancer detected by registries under-represent the total number of cases, and may over-represent the less severe cases or cases from upper socioeconomic strata who are able to afford health care (Babu, 2009).

Our study findings showed that the women several regions of South India present predominately at either stage III and IV. Stage at diagnosis is an important determinant of the overall survival rates. On average, 50% of breast cancer cases in India present at late stage (stage III and IV) (Chopra, 2001). As found in our study, it is very important when women with breast cancer are aware of their disease and how early the treatment can be given. In developed countries like the United states, only 12% of the breast cancer cases are diagnosed at an advanced stage (Goel et al., 1995).

Understanding the previous studies on incidence and prevalence of breast cancer due to various factors helps us understand in detail the modifiable risk factors, which are specific to South India. Primordial prevention can be advocated at the community level to educate the women about breast cancer, ways of dealing with it.

In conclusion, in summary, the study infers to adopt primordial prevention strategies to address the increasing incidence of breast cancer among women. It is important that further explorations including a planned meta analysis of the data would yield comparable results. From the public health perspective, awareness about breast cancer and screening methods to the women have to be expanded. Educational strategies should be aimed modifying the life style, early planning of pregnancy, promoting breast feeding and physical activity. It is very important to obtain reliable data for planning policies, decision-making and setting up the priorities.

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